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K.M

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	19

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/360,242	MCDONALD ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-29,31,32,34-38,40,42,44-46,48-54,57 and 65-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-29,31,32,34-38,40,42,44-46,48-54,57 and 65-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 11,12,13, 14, 16
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

1. Formal Matters

A. Amendment C, filed 9/11/00, has been entered into the record.

B. The Information Disclosure Statements, filed, 3/23/00, 6/29/00, 7/11/00, 8/7/00 and 9/15/00, have been entered into the record. References NC, ND, PM, PT, QF, QH, QJ, which were not initialed on the IDS filed 11/4/99, have now been initialed and included in the initialed references of the IDS's of Papers No. 11, 12, 13, 14 and 16.

6- 12/13/00

C. Claims 26-29, 31-32, 34-38, 40, 42, 44-46, 48-54, 57 and 65-87 are presently pending in this application. Claim 34 is pending but not referred to in the Remarks section.

D. Applicants have stated that they have prepared a Declaration under 37 CFR 1.132. However, at the time of this Action, none has yet been received.

E. It should be noted that numerous claims recite the targeting agent as an antibody, or a compound besides a chemokine. However, in the Office Action dated 11/12/99, Applicants elected the targeting agent as a chemokine and the targeted agent as a toxin. Therefore, all the pending claims have been examined insofar as they read on the elected species of targeting and targeted agents.

F. All 35 USC Statutes not found in this Office Action can be found, cited in full, in a previous Office Action.

2. Information Disclosure Statement

A. Many of the references listed on the Information Disclosure Statements, filed, 3/23/00, 6/29/00, 7/11/00, 8/7/00 and 9/15/00, have not been submitted. Therefore, the references have been lined through, but will be considered upon receipt of the references.

Withdrawn Objections

3. Figures

A. The objections to the Figures have been withdrawn since the Applicants have made the appropriate corrections.

3. Claim Objections

A. All claim rejections have been withdrawn in view of Applicants' amendments to the claims.

Withdrawn Rejections

1. Claim Rejections - 35 USC § 112, second paragraph

A. The rejection of claim 29 under 35 USC 112, second paragraph, regarding the phrase "animal mammal" has been withdrawn since Applicants removed the word "mammal" from the claim.

B. The rejection of claim 40, which was inappropriately cited as claim 43, under 35 USC 112, second paragraph, regarding the phrase "tissue damage-promoting cells" has been withdrawn in view of Applicants' explanation of this phrase.

C. The rejection of claims 44, 45 and 56 under 35 USC 112, second paragraph, regarding the phrase "plurality of" has been withdrawn since Applicants have defined this phrase.

D. The rejection of claim 53 and 63 under 35 USC 112, second paragraph, has been withdrawn since Applicants amended the claim to recite "targeted agent."

2. Claim Rejections - 35 USC § 112, first paragraph - enablement

A. The rejection of claim 40 under 35 USC 112, first paragraph, regarding "tissue damage-promoting cells" has been withdrawn since Applicants have defined the phrase.

B. The rejection of claims 53 and 63 under 35 USC 112, first paragraph, has been withdrawn since Applicants amended the claim to recite "targeted agent."

Maintained Rejections

1. Claim Rejections - 35 USC § 112, first paragraph - enablement

A. Claims 26-29, 31, 32, 34-38, 40, 42, 44-46, 48-54, 57 remain rejected and new claims 65-87 are rejected under 35 USC 112, first paragraph for the reasons already of record on pages 5 and 6 of the Office Action dated 3/2/00. Applicants argue that the claims are not directed to treating every possible disorder associated with an inflammatory response, as the Office Action dated 3/2/00 states, but only toward "pathological conditions associated with inflammatory responses and secondary tissue damage associated with activation, proliferation and migration of immune effector cells." They further argue that "the methods are directed toward treating diseases and disorders that have a common underlying cause, pathophysiological upregulation of cells that participate in pathophysiological immune responses." They also argue that "a specific example of everything within the scope of a broad claim" is not required, nor is the specification required to teach how to treat every inflammatory disorder, but only how to make and use what is claimed without undue experimentation. Finally, a Declaration under 37 CFR 1.132 has been submitted by Dr. McDonald demonstrating the effectiveness of conjugates of chemokine receptor-targeting agents stating the advantage of the claimed method of treatment over prior ligand-toxin therapy.

These arguments have been considered, but are not deemed persuasive for the following reasons. First, Applicants are claiming a method of treating said pathological conditions wherein the disorder or

disease state is selected from the group consisting of CNS injury, CNS inflammatory diseases, neurodegenerative disorders, heart disease, inflammatory eye disease, inflammatory bowel diseases, inflammatory joint diseases, inflammatory kidney or renal diseases, inflammatory lung diseases, inflammatory responses associated with bacterial or viral infections and cytokine regulated cancers. Furthermore, the CNS inflammatory diseases and neurodegenerative disorders are selected from the group consisting of stroke, closed head injury, leukoencephalopathy, choriomeningitis, meningitis, adrenoleukodystrophy, AIDS dementia complex, Alzheimer's disease, Down's Syndrome, chronic fatigue syndrome, encephalitis, encephalomyelitis and spongiform encephalopathies. However, Applicants provide no guidance or working examples of how to treat any or all of these diseases. Applicants only provide *exemplary references* which show the use of animal models which may be used to test chemokine receptor targeting conjugates for the treatment of, for example, SCI (pages 119-125), traumatic brain injury and stroke (pages 125-127), Alzheimer's disease (page 127-128), multiple sclerosis (page 128), arthritis and autoimmune disease (pages 128-132), inflammatory lung disease (pages 133-135), inflammation after gene therapy (135-36), angiogenesis and tumors (page 137-139) and HIV (page 139-142). However, all of these examples only demonstrate some chemokine involvement in the disorder and Applicants have not shown any method of treating all of these diseases, or that any of these "treatments" will have the desired effect. Applicants have not even provided any in vitro or animal data demonstrating the effectiveness in treating any of the claimed disorders, nor do they show a nexus between any in vitro data and one, if not all, in vivo treatments.

In addition, each of these diseases will require a different treatment regimen and, due to the breadth of the diseases and disorders recited in the claims, the treatment regimen would not be predictable to one of ordinary skill in the art. Furthermore, it is not understood how Applicants can treat the claimed disorders of the immune system of a patient by modulating the activation, proliferation and/or migration of inhibited immune effector cells without causing other immune-related problems to occur. Again, while

Applicants describe numerous disease states in which chemokine/toxin conjugates could *potentially* be used, Applicants give no guidance, or working examples for use of these compounds in treating patients who have these diseases. It is not predictable to one of ordinary skill in the art how to treat the disorder of interest without causing subsequent disorders due to an altered immune system. One example well known in the art is that of treating bone marrow cancer in which bone marrow cells are removed from the patient and he/she is administered a dose of chemotherapy in which the patient is brought near death before bone marrow cells are reintroduced. For these reasons, Applicants are not enabled for this method of treatment.

In summary, the breadth of the claims is large with regard to a method of treating disorders associated with inflammatory responses associated with activation, proliferation and/or migration of immune effector cells. In addition, Applicants provide no guidance of how to treat *every* possible disorder associated with an inflammatory response. Also, it is not predictable to one of ordinary skill in the art how to use a method of treating a patient with *any* type of claimed inflammatory response or disease, nor how to treat these diseases without causing subsequent disorders due to an altered immune system. For these reasons, the Examiner maintains that undue experimentation is necessary to practiced the claimed methods of treating all of the said pathological conditions.

B. Claims 29, 31, 32, 34, 38, 40, 42, 44-46, 48-54, 57 and 65-85 are rejected for the reasons already of record for claims 43 and 55 as found on pages 6 and 7 of the Office Action dated 3/2/00 as contain subject matter which is not described in the specification. These claims use the phrase "a portion thereof," or "a sufficient portion." Applicants argue that these claims "further recite that the fragment or portion is effective to facilitate or effect internalization of the conjugate or targeted agent, thereby clearly functionally defining the metes and bounds of 'a portion.'" However, Applicants provide no guidance or working examples of how a portion of a targeting agent and/or a targeted agent can effectively bind to a

cell bearing the necessary receptor and internalize, or how a portion of a targeted agent can treat a disorder associated with inflammatory responses associated with an immune effector cell.

Furthermore, it is also unpredictable to one of ordinary skill in the art as to what portions of said targeting agents have the necessary activity to bind chemokine receptor to cause internalization of the targeting agent/targeted agent conjugate, or what portions of the targeted agents have the necessary activity to produce toxic effects in all cells involved in all disorders. It has been shown that the function of a peptide cannot be determined based solely on knowing the amino acid sequence (see Rudinger et al., 1976, especially the conclusion). The possible effect of changing even one amino acid in a polypeptide can be seen in Cunningham and Wells (1989; Abstract) in which certain single substitutions of alanine in various positions of human growth hormone dramatically altered its binding affinity for the human growth hormone receptor. In addition, George et al. (1988; p. 145) states that: "Sequence-comparison methods will not be able to assess biological relatedness until the structure/function problem is more clearly understood.

In summary, the breadth of the claims is too extensive regarding all portions of all targeting agents. In addition, there is a lack of guidance or working examples of how a *portion*, or a *sufficient portion* of a targeting agent and/or a targeted agent can effectively bind to a cell bearing the necessary receptor and internalize, or how a *portion* of a targeted agent can treat a disorder associated with inflammatory responses associated with an immune effector cell. Furthermore, it is also unpredictable to one of ordinary skill in the art as to what portions of said targeting agents have the necessary activity to bind chemokine receptor to cause internalization of the targeting agent/targeted agent conjugate, or what portions of the targeted agents have the necessary activity to produce toxic effects in all cells involved in all disorders. For these reasons, the Examiner maintains that undue experimentation would be necessary to practice the invention as claimed.

2. Claim Rejections - 35 USC § 102

A. The rejection of claims 26-29, 34-36, 38, 40, 34-45, 47-49, 51, 52 and 57 under 35 USC 102(b) since the Applicants argue that Volk et al. disclose the use of a conjugate of a cytokine, IL-2, not a chemokine, with a toxin as an immunosuppressive agent, not as an anti-inflammatory agent, nor is the conjugate used for inhibition, migration, proliferation, or activation of cells that express chemokine receptors.

3. Claim Rejections - 35 USC § 103

A. The rejection of claims 26-29, 31, 32, 34-38, 40, 42, 44-46, 48-54 and 57 under 35 USC 103(a) have been withdrawn since, while both Ogata et al (1989) and Volk et al (1994) recognize the claimed principle, this art does not enable any method *in vivo* for treating the claimed disorders and diseases.

New Rejections

1. Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A. Claim 65, 68, 69 and 71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 65 is confusing because the phrase "chemokine targeting agent' is not defined in the claims or the specification. It is believed that the phrase should recite "chemokine receptor targeting agent." For this reason, claim 65 recites the limitation "the chemokine targeting agent" into claim 29. There is insufficient antecedent basis for this limitation in the claim. Appropriate correction is required.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
December 18, 2000

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